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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/678,723 | 10/02/2003 | Eduardo Marban | 001107.00459 | 6122 |

22907 7590 07/15/2008

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| EXAMINER | |
|---|---|
| MONTANARI, DAVID A | |
| ART UNIT | PAPER NUMBER |
| 1632 | |
| MAIL DATE | DELIVERY MODE |
| 07/15/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| | | | |
|---|---|---|---|
| ***Office Action Summary*** | **Application No.**<br>10/678,723 | **Applicant(s)**<br>MARBAN ET AL. | |
| | **Examiner**<br>DAVID MONTANARI | **Art Unit**<br>1632 | |

***-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --***

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 October 2007*.
2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-4,6,7,20-39,41,42,46-48 and 76-83* is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *1-4, 6, 7, 20-39, 41, 42, 46-48 and 76-83* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.
10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☐ All b)☐ Some * c)☐ None of:
1.☐ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. Applicants arguments and amendments filed on 10/3/2007 have been entered.
2. Claims 5, 7-19, 40, 43-45 and 49-75 are cancelled.
3. Claims 76-83 are new.
4. Claims 20, 21 and 30 are amended.
5. The oath filed on 4/2/2008 is accepted.
6. The rejection of claims 20 and 30 under 35 USC 112, 2nd parag. is withdrawn.
7. The previous 35 USC 112, scope of enablement rejection is withdrawn in view of the new rejection below.
8. Claims 1-4, 6, 20-39, 41, 42, 46-48 and 76-83 are examined in the instant application.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6, 20-39, 41, 42, 46-48 and 76-83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of modulating calcium channel activity in an excitable cell comprising administering locally to said cell an adenovirus comprising a nucleic acid that encodes the human guanosine triphosphatase protein (GEM), does not reasonably provide enablement for a method of modulating calcium channel activity in any tissue or organ of a mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The breadth of the claimed methods encompasses modulating the activity of a calcium channel in any region of a tissue or organ of a mammal.

While the nature of the invention is a method of modulating L-type calcium channels in cells that have said channel, the art teaches that not all cells possess L-type calcium channels. The art teaches that only excitable cells (i.e. neurons and skeletal muscle or any cell that can propagate action potential) have L-type calcium channels (Lipscombe D., 2002, Circulation Res., Vol. 90(9), pgs. 981-987 see pg. 981, col. 1 lines 1-3 particularly). It is art accepted that non-excitable cells such as fibroblasts, endothelial cells and adipocytes cannot propagate an action potential and thus do not possess L-type calcium channels. This is further detailed in the teachings of Elliott which discuss the difficulties in determining cell calcium entry in non-excitable cells (2001, Cell Calcium, Vol. 30(2), pgs. 72-93).

Whereas the working examples all teach the delivery of a recombinant adenovirus comprising a gene encoding for mammalian GEM into the hearts of mice, guinea pigs and swine the specification fails to teach the delivery and modulation of activity of a calcium channel in all tissue and cell types. The art above is clear that L-type calcium channels are only in excitable cells and the specification teaches that the GEM protein only interacts with specific subunits of the L-type calcium channel (pg. 8 lines 28-31).

Thus in view of the teachings in the specification and the art above limiting the claimed invention to a method of modulating calcium channel activity in an excitable cell comprising administering locally to said cell an adenovirus comprising a nucleic acid that encodes the human guanosine triphosphatase protein (GEM) is proper.

Claims 1-4, 6, 20-39, 41, 42, 46-48 and 76-83 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

When the claim is analyzed in light of the specification, the instant invention encompasses proteins that share a 70% protein sequence with SEQ ID NO: 1. The specification teaches (parag. 0137):

> “As discussed, the invention methods can be used with recombinant adenoviruses that encode a mammalian Gem protein or a variant thereof. By "variant" is meant a nucleic acid sequence that encodes protein with at least about 70% sequence identify to the protein sequence shown above as SEQ ID NO. 1, preferably at least about 80%, more preferably at least about 90% or more up to about 99% identical.”

In view of this teaching the specification has failed to teach possession of any protein that is less than 100% sequence identical with SEQ ID NO: 1 that exhibits modulation of a calcium channel in a cell. The specification provides no description of any sequence other than SEQ ID NO: 1 that would indicate possession at the time of filing. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, only SEQ ID NO:1 is sufficiently described to indicate possession of a gene that encodes a product capable of modulating calcium channel activity. The specification does not provide any disclosure as to what the complete structure would be of any gene other than the one disclosed in SEQ ID NO:1. The specification teaches no structural analysis for said gene. Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only characteristic described, is that the protein represented in SEQ ID NO:1 modulated calcium channel acitivty. The specification does not teach any other identifying characteristic or any other related sequences that would guide the artisan to contemplate other genes that would be encoded by less than the full sequence represented in SEQ ID NO:1.

Applicants' attention is directed to the decision in In re Shokal, 113, USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim, In re Soll, 25 C.C.P.A. (Patents) 1309, 97, F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such a number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as halogens, consisting of four species, a reduction in practice of three, or perhaps even two, might server to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that applicant is in possession of any protein that will modulate calcium channel activity.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 29 in line 3 recites "a packaging site (.psi)", however this is generally unclear with respect to what is being claimed. If the Applicant means a "packaging sequence" then this would provide sufficient clarity to the recombinant adenovirus.

## *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6, 20-21, 27-29, 31-34, 41, 42 and 76-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wright et al. (2001, Basic Res. Cardiol., Vol. 96, pgs. 227-236) and Beguin et al., (2001, Nature, Vol. 411, pgs. 701-706).

Wright et al. teach a method of in vivo myocardial gene transfer using a recombinant adenovirus, driven by the CMV promoter and expression the LacZ or beta-gal reporter genes (pg. 227, Abstract 1st parag. and pg. 231 col. 2 last sentence). Wright continues to teach that the transfer and expression of genes in the heart is a promising research tool and therapy, is commonly achieved by direct intra-myocardial injection and that cardiac myocytes in vivo can express reporter genes for at least 30 days post injection (pg. 227, col. 1). Wright continues to teach that $1x10^{10}$ pfu of recombinant adenovirus was administered to rabbit hearts (pg. 230, Table 1 and pg. 231 col. 2 last sentence and pg. 231 Fig. 1) resulting in broad expression with peak expression occurring at day 3 post-injection (pg. 232, Fig. 2). Wright summarizes that direct intramyocardial injection with recombinant adenovirus results in reliable transgene expression (pg. 233, col. 2 parag. 2 lines 1-5). Wright et al. does not teach a method of delivering a recombinant adenovirus encoding the GEM protein.

Beguin et al. teach that the GTP-bound form of kir/GEM (a Ras-related small G-protein) inhibits high-voltage-activated calcium channel activity by interacting directly with the beta-subunit (pg. 701, Abstract). Beguin continues to teach that inhibition of L-type calcium channels by kir/GEM prevents calcium triggered exocytosis in hormone-secreting cells and propose that kir/GEM interacts with beta-subunits regulating calcium channel expression at the cell surface (pg. 701, Abstract, last four lines). Beguin summarizes that kir/GEM could have a protective effect against an overload of calcium (toxicity) that impairs a variety of cellular functions and may also inhibit cell proliferation by reducing calcium-mediated cell growth (pg. 705, col. 1 parag. 1, last four lines). Beguin et al. do not teach a method of modulating activity of a calcium channel in the heart of a mammal.

Thus the ordinary artisan would have been motivated at the time of filing to make and use the invention as claimed given the combined teachings and motivations of Wright and Beguin. Wright provides teaching to the ordinary artisan to deliver and express exogenous proteins in cardiac cells, but demonstrating a detailed protocol of injections, dosage and time course. Motivation is provided to the ordinary artisan by Wright teaching that direct intramyocardial injection results in reliable transgene expression. Additional teaching and motivation is provided by Beguin teaching that kir/GEM inhibits calcium channels by directly interacting with the beta-subunit of said channel. Motivation is provided by Beguin to use kir/GEM in vivo in teaching that kir/GEM could have a protective effect against cell calcium overload as well as inhibiting cell proliferation. Thus the cited art provides the requisite teachings and motivations to make and use the invention as claimed.

Claims 1, 20-26 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wright et al. (2001, Basic Res. Cardiol., Vol. 96, pgs. 227-236), Beguin et al., (2001, Nature, Vol. 411, pgs. 701-706), Krougliak et al. (2001, J Gene Med., Vol. 3, pgs. 51-58) and Li et al., (2001, Cancer Research, Vol. 61, pgs. 6428-6236).

Wright et al. teach a method of in vivo myocardial gene transfer using a recombinant adenovirus, driven by the CMV promoter and expression the LacZ or beta-gal reporter genes (pg. 227, Abstract 1st parag. and pg. 231 col. 2 last sentence). Wright continues to teach that the transfer and expression of genes in the heart is a promising research tool and therapy, is commonly achieved by direct intra-myocardial injection and that cardiac myocytes in vivo can express reporter genes for at least 30 days post injection (pg. 227, col. 1). Wright continues to teach that $1x10^{10}$ pfu of recombinant adenovirus was administered to rabbit hearts (pg. 230, Table 1 and pg. 231 col. 2 last sentence and pg. 231 Fig. 1) resulting in broad expression with peak expression occurring at day 3 post-injection (pg. 232, Fig. 2). Wright summarizes that direct intramyocardial injection with recombinant adenovirus results in reliable transgene expression (pg. 233, col. 2 parag. 2 lines 1-5). Wright et al. does not teach a method of delivering a recombinant adenovirus encoding the GEM protein.

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parag. 1, last four lines). Beguin et al. do not teach a method of modulating activity of a calcium channel in the heart of a mammal.

Krougliak et al. teach using a cre/lox recombinase system in a recombinant adenovirus to stably deliver transgenes into a genome (pg. 51, Abstract, 2nd parag.). Krougliak continues to teach that they have developed "an adenovirus vector that can be used to deliver a self-excising, self-replicating episome that then will be maintained extrachromosomally even in dividing cells in immunocompetent animals." (pg. 52, col. 1 parag. 2, lines 1-6). Krugliak continues they accomplished this by combining "Epstein-Barr virus (EBV)-derived replicative elements, a tetracycline (Tc)-inducible expression system (Tet-off), and the Cre-lox recombination system in the context of an E1/E3/E4-deleted adenovirus vector" (pg. 52, col. 1 parag. 2 lines 7-10). Krougliak continues to teach that the final size of the vector was 37.8 kb (pg. 54, col. 2, parag. 2 lines 9 and 10). Krougliak et al. does not teach a method of modulating calcium channel activity.

Li et al. teach that "To control both *E1A* and *E1B* genes with single AFP, an EMCV IRES structure was applied to build an artificial E1A-IRES-E1B bicistronic expression cassette.", and that the EMCV IRES has been well characterized and applied for mediating secondary gene expression (pg. 6430, col. 1 parag. 2, lines 1-5). Li continues to teach that "This artificial E1A-IRES-E1B bicistronic cassette enables both E1A and E1B to form a single unit for transcription, whereas the IRES structure gives the internal translation initiation for E1B translation." (pg. 6430, col. 1 parag. 2 lines 5-8). Li continues to teach that the "E1A proteins transactivate both viral and cellular genes critical for productive viral injection including E1B, E2 and E4" (pg. 6428, col. 2 parag. 2 lines 5 and 6). Li et al. do not teach a method of modulating calcium channel activity.

Thus the ordinary artisan would have been motivated at the time of filing to make and use the invention as claimed given the combined teachings and motivations of Wright, Beguin, Krougliak and Li. Wright provides teaching to the ordinary artisan to deliver and express exogenous proteins in cardiac cells, but demonstrating a detailed protocol of injections, dosage and time course. Motivation is provided to the ordinary artisan by Wright teaching that direct intramyocardial injection results in reliable transgene expression. Additional teaching and motivation is provided by Beguin teaching that kir/GEM inhibits calcium channels by directly interacting with the beta-subunit of said channel. Motivation is provided by Beguin to use kir/GEM in vivo in teaching that kir/GEM could have a protective effect against cell calcium overload as well as inhibiting cell proliferation. Additional teaching and motivation is provided by Krougliak and Li teaching that cre/lox recombinase can result in the stable expression of a transgene and that IRES sites are beneficial for mediating bicistronic expression. Thus the cited art provides the requisite teachings and motivations to make and use the invention as claimed.

Claims 1, 35-37 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wright et al. (2001, Basic Res. Cardiol., Vol. 96, pgs. 227-236), Beguin et al., (2001, Nature, Vol. 411, pgs. 701-706), Maguire et al. (1994, Science, Vol. 265, pgs. 241-244) and Finlin et al., (2000, Biochem J., Vol. 347, pgs. 223-231).

Wright et al. teach a method of in vivo myocardial gene transfer using a recombinant adenovirus, driven by the CMV promoter and expression the LacZ or beta-gal reporter genes (pg. 227, Abstract 1st parag. and pg. 231 col. 2 last sentence). Wright continues to teach that the transfer and expression of genes in the heart is a promising research tool and therapy, is commonly achieved by direct intra-myocardial injection and that cardiac myocytes in vivo can express reporter genes for at least 30 days post injection (pg. 227, col. 1). Wright continues to teach that $1 \times 10^{10}$ pfu of recombinant adenovirus was administered to rabbit hearts (pg. 230, Table 1 and pg. 231 col. 2 last sentence and pg. 231 Fig. 1) resulting in broad expression with peak expression occurring at day 3 post-injection (pg. 232, Fig. 2). Wright summarizes that direct intramyocardial injection with recombinant adenovirus results in reliable transgene expression (pg. 233, col. 2 parag. 2 lines 1-5). Wright et al. does not teach a method of delivering a recombinant adenovirus encoding the GEM protein.

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Maguire et al. teach the full-length amino acid sequence of human and mouse GEM (pg. 241, Fig. 1). Maguire et al. do not teach a method of modulating activity of a calcium channel in the heart of a mammal.

Finlin et al. teach a method of deleting amino acids sequences of differing length in the GTP-binding protein Rem2 (pg. 223, Abstract). Finlin continues to teach that deleting a large portion of the C-terminus of Rem2 resulted in its redistribution in the cytosol (pg. 223, Abstract). Finlin et al. do not teach a method of modulating activity of a calcium channel in the heart of a mammal.

Thus the ordinary artisan would have been motivated at the time of filing to make and use the invention as claimed given the combined teachings and motivations of Wright, Beguin, Krougliak and Li. Wright provides teaching to the ordinary artisan to deliver and express exogenous proteins in cardiac cells, but demonstrating a detailed protocol of injections, dosage and time course. Motivation is provided to the ordinary artisan by Wright teaching that direct intramyocardial injection results in reliable transgene expression. Additional teaching and motivation is provided by Beguin teaching that kir/GEM inhibits calcium channels by directly interacting with the beta-subunit of said channel. Motivation is provided by Beguin to use kir/GEM in vivo in teaching that kir/GEM could have a protective effect against cell calcium overload as well as inhibiting cell proliferation. Additional teaching and motivation is provided by Maguire and Finline teaching that full-length amino acid sequence of human and mouse GEM as well as that deleting amino acids in a protein sequence can be used to study how function of the protein can be altered. Thus the cited art provides the requisite teachings and motivations to make and use the invention as claimed.

Claims 38 and 46-48 are free of the prior art.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DAVID MONTANARI whose telephone number is (571)272-3108. The examiner can normally be reached on M-Tr 8-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 1-571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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